Remarks/Arguments

The foregoing amendments include a statement of priority claim and the cancellation of non-elected claims, and do not add new matter.

Restriction and Election of Species

In response to the restated Restriction and Election of Species requirement, Applicants reaffirm the election of the invention of Group IV (58-66), with traverse. Applicants further reaffirm election of the following species, also with traverse:

Subgroup 1: Species of target protein - tissue necrosis factor receptor (TNF receptor). Support for this election is at least at page 9, lines 8-12. Claims 58, 59, 61, and 65 read on this species.

Subgroup 2: Species of ligand - a ligand that forms a disulfide bond with the target protein. All claims pending read on this species.

Subgroup 3: Species of a chemically reactive group - a thiol group. All claims pending read on this species.

The traversal is on the grounds submitted in Applicants previous response dated December 16, 2002 (Paper No. 8).

Information Disclosure Statement

Enclosed is a Supplemental Information Disclosure Statement providing the publication dates for the publications numbered 16 and 20 in the Information Disclosure Statement of record. The current submission is in full compliance with 37 CFR 1.97(e).

Specification

The application has been supplemented with a specific reference to the parent application, the priority of which is claimed in the present divisional case.

Priority/New Matter Rejection

Claims 58-61 and 65 were rejected under 35 U.S.C. 112, first paragraph, as allegedly containing new matter. The Examiner noted that the support pointed out by Applicants did not provide specific support for "all" of the limitations in "all" of the claims added, such as applicants did not point out specific support for the "inorganic" ligands that would be encompassed by claim 58. Accordingly, October 17, 2001 was accorded as the effective filing date of the claims pending.

Applicants submit that all claims currently pending are fully supported by the specification as originally filed and are, therefore, entitled to the June 26, 1998 priority. For the Examiner's convenience, locations for support are indicated in the table below.

Claim	Phrase	Support
58	a ligand less than 2000 daltons in size	at least at page 6, lines 10-21; and page 16, line 26
58	that binds covalently to a chemically reactive group at a site of interest on a target protein to form a target protein-ligand conjugate	at least at page 3, lines 28-31; page 4, lines 15-20; page 14, line 24 - page 15, line 14; and original claim 1
58	detecting the formation of said target protein-ligand conjugate by mass spectrometry analysis	at least at page 21, lines 7-25
59	wherein the ligand is less than 1500 daltons in size	at least at page 16, line 27
61	wherein the ligand is less than 750 daltons in size.	at least at page 16, line 27
62	wherein said target protein is a protease.	at least at page 8, line 24
63	wherein said target protein is a kinase.	at least at page 8, lines 26-27
64	wherein said target protein is a dephosphorylase (phosphatase)	at least at page 8, line 27

65	wherein said target protein is a TNF receptor	at least at page 8, lines 30-31; page 9, lines 9-10, and original claim 4
66	wherein said target protein is mdm2 receptor	at least at page 9, line 10

As the claims do not recited an "inorganic ligand," no specific support is needed for that phrase.

From the foregoing table it should be clear that all claims under examination are fully supported by the specification as originally filed, therefore, the present new matter rejection should be withdrawn, and the application should be accorded the priority of June 26, 1998. As this is not a continuation-in-part application, the filing of a new Oath or Declaration is not necessary.

Rejection under 35 USC 112, first paragraph - Written Description

Claims 58-61 and 65 were rejected under 35 USC 112, first paragraph for alleged lack of sufficient written description for the genus claimed. The Examiner specifically noted that

1. no structural features or identifying characteristics are provided for the "ligands" (the Examiner could find no support for "inorganic ligands"), "chemically reactive groups" or "target proteins";

2. no guidance is provided for determining the "site of interest" on the target protein;

3. the specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form the "ligands" or the "chemically reactive groups;" and

4. no structural or identifying features have been set forth for the "target proteins."

According to the Examiner, the disclosure "fails to describe the common attributes or characteristics that identify ***all*** of the members of the genus or even a substantial portion thereof,

and because the genus is enormous and highly variant, simply reciting a "laundry list" of potential ligands, chemically reactive groups and target proteins . . . is insufficient to teach the entire genus."

Applicants respectfully disagree and vigorously traverse the rejection

The Legal Standard

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. § 112, first paragraph is whether the disclosure "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." In re Kaslow, 707 F.2d 1366, 1375, 212 USPQ 1089, 1096 (Fed. Cir. 1983); see also Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See, e.g. Vas-Cath, 935 F.2d at 1563; 19 USPQ2d at 1116. The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. Union Oil v. Atlantic Richfield Co., 208 F.3d 989, 996 (Fed. Cir. 2000).

In Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1566, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997), the Federal Circuit held that an adequate written description of genetic material "requires a precise definition, such as by structure, formula, chemical name, or physical properties." A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequences, falling within the scope of the genus or a recitation of structural features to the members of the genus, which features constitute a substantial portion of the genus. *Id.* 119 F.3d at 1569, 43 USPQ2d at 1406. The Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, & 1, 'Written Description' Requirement, 66 F.R. 1099, 1106 (January 5, 2001) (hereinafter "Written Description Guidelines") provide that applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed

correlation between function and structure, or some combination of such characteristics. Written Description Guidelines at 1106.

The Claimed Invention

It is axiomatic that the requirements of patentability, including the written description requirement, must be assessed with regard to the invention claimed. The present invention is not directed to target proteins, or ligands. Rather, the present invention concerns broadly applicable screening methods for rapidly identifying ligands, less than 2000 daltons in size, of a target protein that can form a covalent bond with a chemically reactive group on the target protein at a site of interest, by detecting the formation of the target protein-ligand conjugate by mass spectrometry.

It is clear from the disclosure that this method can be used to identify small molecule ligands (e.g. ligands less than 2000 daltons in size) of "virtually any peptide or protein that comprises two or more amino acids and which possesses or is capable of being modified to possess a chemically reactive group for binding to a small organic molecule." (Page 8, lines 15-19.) While proteins of interest are listed on pages 8-9 and other locations in the application, the operability of the invention is not limited to any particular protein structure. The claimed method is suitable for identifying ligands of any protein that contains or is capable of being modified to contain a chemically reactive group, e.g. a thiol group, that can form a covalent bond with a ligand candidate.

Conversely, the operability of the claimed invention is not limited to any particular ligand. The claimed method is suitable for screening any ligand, individually or as part of a library, regardless of its overall chemical structure, as long as it contains a reactive group capable of forming a covalent bond with a chemically reactive group on a target protein. Chemical classes of ligands are listed, for example, on page 17, lines 5-18, however, any small molecule, less than 2000 daltons in size, can be screened by the methods of the present invention, within or outside the specifically listed chemical classes, if a covalent bond can be formed between such ligand and a chemically reactive group on a target protein. As it is stated at page 17, lines 18-23: "In fact, virtually any small organic molecule that is capable of covalently bonding to a known

chemically reactive functionality might find use in the present invention with the proviso that it is sufficiently soluble and stable in aqueous solution to be tested for its ability to bind to the biological target molecule."

The disclosure is also clear that those "of skill in the art will be capable of covalently linking a chemically reactive group-containing compound to a target biomolecule through virtually any type of covalent bond, including . . .disulfide bond . . .. (Passage bridging pages 13-14.) Although the nature of the covalent group is not critical, the disclosure provides an extensive listing of chemically reactive groups, e.g. at page, 9, lines 16-20; page 15, lines 3-13, and page 17, lines 5-23. Applicants also provide guidance for choosing compatible chemically reactive groups on the target proteins and ligands (see, e.g. page 16, lines 4-23 and the passage bridging pages 17-18).

Finally, the "site of interest" on the target protein is just that; any site to which the binding of a ligand is desirable. As applicants explain on page 15, line 15 - page 16, line 3: "Thus, it is expected that by screening mixtures of two or more organic compounds against a chemically reactive group at a site of interest on a target biomolecule, those organic compounds having the highest non-covalent affinity for the site of interest will be capable of most efficiently forming covalent bonds with the chemically reactive group at that site. In this manner, one can determine which library members have the highest relative binding affinity for the site being tested, wherein that binding affinity is directly related to the ability of those compounds to form covalent bonds with the chemically reactive group at the site of interest."

The invention is further illustrated by a working example, where the target protein is a cysteamine-modified thymydilate synthase, and the ligands are aldehydes. The "site of interest" is the active site of the protein. The aldehyde functionality of the individuals ligands reacts with the primary amine group of the protein-bound cysteamine to yield an imine bond. Because this reaction is reversible, equilibrium will favor imine formation with the library member that had the highest intrinsic affinity for the active site of the protein.

Proper Application of the Legal Standard

The Examiner's reasoning underlying the present rejection indicates that the Examiner erroneously applied the legal standard developed for assessing written description for a genus of chemical entities (e.g. nucleic acid molecules or proteins) to an invention which provides a new screening assay. The Examiner has given no reason why one skilled in the art would not reasonably accept that the screening method of the invention can be performed with any target protein and any ligand, capable of forming any type of covalent bond, i.e. that applicants were in the possession of the invention at the effective filing date of the present application, within the full scope of the claims pending. Indeed, such reasons do not exist. The reactive groups and chemical reactions involved in the formation of the covalent bond between a target protein and a ligand, as required by the claims, were well known in the art at the priority date of the present application, and are also detailed in the specification, including the references cited therein. Techniques and instruments of mass spectrometry were also known and are taught in the specification. There is no reason, and the Examiner certainly did not provide one, why these steps could not be performed with virtually any protein and any ligand, following well known steps and reactions of chemistry.

The burden is on the Examiner to provide specific reasons why Applicants did not provide sufficient written description for the invention claimed. It is submitted that the Examiner failed to provide such reasoning. Accordingly, the Examiner is respectfully requested to withdraw the present rejection, or, as a minimum, if the rejection is upheld, provide specific scientific reasoning why one skilled in the art would not accept that at the effective filing date of the present application applicants were in the possession of the invention as claimed.

Additional Remarks

As discussed above, the disclosure of specific protein or ligand structures is not needed for adequate written description. However, the Examiner's assertions that such structures are missing are misplaced. The listing of specific target proteins, e.g. in the passage bridging pages 8

and 9, is equivalent with providing structures for the listed proteins, since such proteins, including their structures, were well known in the art at the priority date of the present application.

Chemically reactive groups are detailed at locations provided in the foregoing table.

Although complete ligand structures are not specifically disclosed, the ligands are sufficiently characterized to the extent necessary to perform the present invention, by listing exemplary chemical classes, and exemplary reactive groups that can bind to a compatible reactive group on the target protein, to form a covalent bond.

Finally, as noted before, the "site of interest" can be any site on a target protein, e.g. an active site, as demonstrated in the Example.

Applicants are at a loss to understand the Examiner's reference to the extensive teaching in the specification as a "laundry list" of potential ligands, etc. It is hard to imagine how else Applicants could provide guidance in the specification but by providing an extensive listing of exemplary embodiments within the scope of the invention.

Claim Rejections - 35 USC 102

Claims 58-61 were rejected under 35 USC 102(b) "as being anticipated" by Erlanson et al., August 15, 2000. The rejection is based on the assumption that the effective filing date of the present application is October 17, 2001.

Claim 60 has been canceled. The rejection of claims 58, 59 and 61 is respectfully traversed.

As Applicants have shown that the application is entitled to the priority date of June 26, 1998, Erlanson et al. is not prior art, and the present rejection is moot.

Claim Rejections - 35 USC 103(a)

(1) Claims 58-61 were rejected under 35 USC 103(a) under U.S. Patent No. 5,367,058 (Pitner et al.) and Ganem et al., J. Am. Chem. Soc. 1991, 113(16), 6294-6.

Pitner et al. was cited for its alleged disclosure of identifying ligands less than 2000 daltons in size by binding to a target protein at a site of interest, while Ganem et al. was cited for its disclosure of mass spectrometry as a detection method, suitable to identify a ligand.

The proposed combination of references is legally improper

Pitner et al. concerns the modification of antibodies with affinity labeling reagents. In particular, the antibodies are modified near to their antigen binding site, e.g. by the addition of a thiol group, so that a covalent group can be formed between the antibody and an antigen binding to the antibody. This approach is stated to increase the affinity of the antibody for its antigen, as compared to the affinity of a corresponding unmodified antibody to the antigen.

Ganem et al. propose the use of mass spectrometry for the detection of ***noncovalent*** molecular association complexes.

Since antibodies are raised against antigens, the antigen of any particular antibody is, by definition, known. Accordingly, one reading the disclosure of Pitner et al. would not be motivated to search for any method for identifying the antigens present in the antigen-antibody complexes, given the fact that the antigens are known.

Furthermore, Pitner et al. disclose a covalent bond between an antibody and an antigen, while Ganem et al. deal with the detection of non-covalent complexes. Therefore, one reading the disclosure of Pitner et al., even if for some reason the identification of the (already known) antigen were desirable, would not turn to Ganem et al., addressing a completely different problem.

The references, even if combined, would not make obvious the claimed invention

Since Pitner et al. has no disclosure of any detection method, and Ganem et al. teaches the use of mass spectrometry to detect weak, non-covalent complexes, the combination of the two references, even it is were proper, does not teach the detection of the formation of a covalent target protein-ligand conjugate by mass spectrometry analysis, as required by the language of the rejected claims.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(2) Claims 58-61 have been rejected under 35 USC 102(a) over Pitner et al. and Loo, *Mass Spectrometry Reviews*, 1997, 16, 1-23. Pitner et al. was applied as discussed above. Loo was cited for allegedly teaching the identification of novel protein-ligand interactions, including antibody-antigen conjugates, by mass spectrometry.

The rejection is respectfully traversed.

Pitner et al. has been discussed above. Loo concerns the study of ***noncovalent*** protein complexes by electrospray ionization mass spectrometry.

Just as in the previous rejection, *the proposed combination of the cited references is legally improper,* since neither reference has any motivation for the purported combination.

Since antibodies are raised against antigens, the antigen of any particular antibody is, by definition, known. Accordingly, one reading the disclosure of Pitner et al. would not be motivated to search for any method for identifying the antigens present in the antigen-antibody complexes, given the fact that the antigens are known.

Furthermore, Pitner et al. disclose a covalent bond between an antibody and an antigen, while Loo deals with the detection of non-covalent complexes. Therefore, one reading the disclosure of Pitner et al., even if for some reason the identification of the (already known) antigen were desirable, would not turn to Loo, addressing a completely different problem.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Double Patenting

Claims 58-61 and 65 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-14 of U.S. Patent No. 6,335,155, over claims 1-39 of U.S. Application Publication No. 2002/0081621 A1; over claims 1-30 of U.S. Application Publication No. 2002/0155505; over claims 1-39 of U.S. Application Publication No. 2002/0022233; and over claims 1-39 of U.S. Application Publication No. 2003/0013125. The rejections over the pending applications are provisional, since the allegedly conflicting claims have not yet been patented.

The attached Terminal Disclaimer is believed to overcome all obviousness-type double patenting rejections.

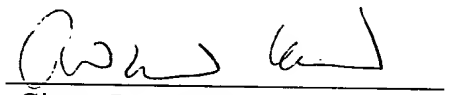
The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Should the Examiner find that there are any further issues outstanding, Applicants hereby request a personal interview. The Examiner is respectfully requested to contact the undersigned attorney to arrange the time for the interview.

The Commissioner is hereby authorized to charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39750-0002DV1). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: April 18, 2003



Ginger R. Dreger
Reg. No. 33,055

HELLER EHRMAN WHITE & McAULIFFE LLP
Customer No. 25213
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638